REMARKS

Amendments to the Claims

Claim 9 has been canceled without prejudice.

Claims 2, 5, 8, 10, 21, 22, 27, 28 and 89 have been amended.

New Claims 93-96 have been added.

Claims 2 and 22 have been amended to recite that the uncoupled resorbing bone is "non-fractured" to better clarify the claimed invention. Support for this amendment can be found in the Specification, for example, at page 12, lines 24-25 and page 13, lines 23-25.

Claims 5, 8, 10 and 28 have been amended to clarify that the bone is an uncoupled resorbing bone. Support for this amendment can be found in the Specification, for example, at page 12, lines 20-21.

Claims 21 and 22 has been amended to recite administration into "at least one" uncoupled resorbing bone. Support this amendment can be found in the Specification, for example, at Claim 1 as originally filed and page 54, lines 1-3.

Claim 27 has been amended to recite REMICADE® infliximab. Support for this amendment can be found in the Specification, for example, at page 29, line 28 to page 30, line 23.

Claim 89 has been also amended to reflect that the anti-resorptive agent remains in the bone in an effective amount for at least month. New Claims 94 and 96 have been added reciting methods wherein the formulation remains in the bone in an effective amount for at least one month. New Claim 95 has been added reciting a method of Claim 60 wherein the device is adapted to deliver the bone forming agent and the anti-resorptive agent into the vertebral body for at least one month. Support for these amendments and the new claims can be found in the Specification, for example, at page 16, line 21 and lines 28-30.

New Claim 93 has been added to recite the method of Claim 1 wherein the bone is osteoporotic or osteopenic. Support for this amendment can be found in the Specification, for example, at page 12, lines 21-24.

No new matter has been added. Entry of these amendments and new claims is respectfully requested.

Rejection of Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89, 91 and 92 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89, 91 and 92 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention. The Office Action alleges that it is unclear whether the administration of a bone forming agent and antagonist of TNF-α is to all the bones of body or to any specific bone, and that it is not clear how treatment is possible for all the intact bones of a human body (*see* the Office Action at page 3, first paragraph). Applicants respectfully disagree.

The focus of the claim analysis must be on the actual terms of the claim. Independent Claims 1, 70 and 89 each recite a "method of therapeutically treating an uncoupled resorbing bone in a patient" comprising administering a formulations into "the bone". Therefore, administration into just one bone could be sufficient to practice the claimed method and to fall within the scope of the claims. Administering the formulations into multiple bones could constitute practicing the claimed method multiple times.

Claims 21 and 22 have been amended to recite that the recited formulation is administered into "at least one" uncoupled resorbing bone. Therefore, administration into just one bone could be sufficient to practice the claimed method and to fall within the scope of the claims. Administering the formulations into multiple bones could constitute practicing the claimed method multiple times.

The Office Action states that the term "into the bone" is indefinite especially in light of the limitation intact bone. According to the Office Action, "since all bones are intact in [the] body, the administration to which part/specific bone of [the] body is not defined and thus it is unclear (considering the fact that there are around 208 bones in [the] human body)." Applicants respectfully disagree.

The claim terms "uncoupled resorbing bone" and "intact" must be read in light of the specification. *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005), cited in MPEP § 2111. Here, Claims 1, 70 and 89 are directed to treating an "uncoupled resorbing bone". The specification clearly indicates that such a bone may be intact (*i.e.*, not fractured) or fractured, and it may or may not be osteoporotic:

> Because osteoporosis is a continuous process, the bone to which the therapeutic drug is administered may be in any one of a number of states. In general, the bone should be

> characterized as uncoupled resorbing bone. For the purposes of the present invention, the bone remodeling processes in "uncoupled resorbing bone" are such that bone resorption exceeds bone formation, thereby leading to osteopenic and eventually, in some cases, osteoporotic bone. Accordingly, the bone may be an intact bone or it may be fractured (such as a vertebral body compression fracture). It may be osteoporotic (defined as having a bone mineral density (BMD) of at least 2 standard deviations below normal bone mineral density for that patient's age and sex), it may be osteopenic or it may have normal bone mineral density (BMD). In some instances, the uncoupling has existed for a time sufficient to produce osteoporotic bone. In other instances, the uncoupling has existed for only a relatively short time and so the bone is osteopenic or normal. Accordingly, the bone may be an intact bone or it may be fractured (such as a vertebral body compression fracture). (Specification, for example, at page 12, line 19 - page 13, page 2, emphasis added).

Therefore, not all uncoupled resorbing bone bones must be intact (non-fractured) in the body, some may be fractured. Thus, the fact that Claims 2 and 22 are directed to administration into an uncoupled resorbing bone that is not fractured (intact) in no way renders the term "uncoupled resorbing bone" unclear. Dependent claims contain all of the limitations from the claim from which they depend, plus at least one further limitation (*see* 35 U.S.C. 112, paragraph 4). Dependent Claims 2 and 22 properly contain the further limitation that the uncoupled resorbing bone is not fractured (intact). To expedite prosecution, Claims 2 and 22 have been amended to recite that the bone is "non-fractured," instead of "intact" to better clarify the invention.

It is noted that Claim 1 has recited "[a] method of therapeutically treating an uncoupled resorbing bone" since the application was originally filed, and Claim 2 has recite "the method of Claim 1 wherein the bone is intact" since in the application was originally filed, yet the claims have never been rejected on these grounds before now, despite the issuance of multiple Office Actions. Section 706 of the *Manual of Patent Examining Procedure* provides that "[t]he goal of examination is to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise reply completely at the earliest opportunity." This goal has not been met with regard to this late rejection. Applicants traverse the rejection on this additional ground as well.

Particularly as amended, the claims are clear and definite and define the scope of the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89 and 91-92 Under 35 U.S.C. §103(a)

Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89 and 91-92 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radomsky (U.S. Patent No. 5,942,499, hereinafter, "Radomsky") in view of Allali *et al.* (*Ann. Rheum. Dis.* 62: 347-349 (2003), hereinafter, "Allali"), Bertolini *et al.* (*Nature*, 3196 (1986), hereinafter, "Bertolini", and Brandt *et al.* (*Arthritis and Rheumatism* 43:1346-1352 (2000), hereinafter, "Brandt") or vice versa.

According to the Office Action:

> One of skill in the art would have recognized that the results of the combination [of these references] would have yielded nothing more than predictable results one of ordinary skill in the art at the time the invention was made, as demonstrated by the teachings of the Radomsky and Allali and Berlini and Brandt's publication. Since Radomsky teaches administration [of] the bone forming agent to bone, it would have been obvious to one of ordinary skill to administer the bone forming agent and antiresorptive agent such as infliximab to hip or any vertebral part of [the] body. By utilizing infliximab, one of ordinary skill would have expected treatment of osteoporotic bone in a patient by administering infliximab in an uncoupled resorbing bone because Allali and Brand teaches that infliximab has been show to mediate the increase of bone resorption in osteoporosis related deficiency. (Office Action, pages 5-6).

Applicants respectfully disagree because the combination of references do not teach or suggest the combination of bone forming agents (BFA) and an anti-resorptive agent (ARA) in the treatment of uncoupled resorbing bone, nor does it teach administration of an ARA into the the bone.

Teachings of the Cited References

Radomsky

Radomsky discloses a composition comprising hyaluronic acid (HA) and a growth factor for promoting bone growth (*see* col. 1, line 19 and lines 34-39). Radomsky discloses that the composition can be applied to the desired site of bone growth, including vertebral compression fractures (col. 2, lines 50-58). Radomsky also teaches that the composition must persist at the site of desired bone growth for a period from about three (3) to about thirty (30) days, typically from three (3) to about fourteen (14) days (col. 2, lines 27-30). However, Radomsky teaches that: "If the composition persists at the site of desired bone growth for an excessive period, its

presence at the bone site may inhibit the natural development of the bone, sometimes resulting in no bone formation at all" (col. 2, lines 33-36).

Allali

Allali reports an increase in the bone mineral density (BMD) of patients with spondyloarthropathy (SpA) treated systemically with REMICADE® infliximab by infusion. Significantly, Allali does not disclose the local administration of selective cytokine inhibitors. (See Applicants' specification, page 3, lines 21-28). Allali notes that "the cause of SpA associated osteoporosis remains controversial". (page 348, column 2), Allali reports on a study in which TNF-α inhibition resulted in a decrease systemic inflammation and an increase in bone density, and indicates that this study adds evidence in favor of the hypothesis of bone loss mainly due to systemic inflammation through direct effects of TNF on bone. Allali also suggests that other factors, such as increased patient mobility, may explain the increase in BMD, and notes that changes in biochemical parameters of bone turnover and BMD were not correlated. In short, Allali teaches that bone loss is caused by TNF-α's effects on systemic inflammation, and only teaches treatment by systemic infusion. Nothing in Allali teaches or suggests administration of a TNF-α inhibitor into the bone, and, in fact, Allali's focus on systemic effects and treatment teaches away from such local administration.

Bertolini

Bertolini is a 1986 paper reporting on *in vitro* that it stated may suggest that interleukin-1, TNF-α TNF-β may play a role in bone resorbing activity. Specifically, Bertolini reported that *in vitro* treatment of fetal rat bone cultures with recombinant human TNF-α and TNF-β caused osteoclastic resorption and inhibited bone collagen synthesis, and suggested that at least part of the bone-resorbing activity present in activated leukocyte culture supernatants may be due to these cytokines. (*See* Bertolini, Abstract and at page 516, left col., second full paragraph). Bertolini did not teach a clear cause-and-effect relationship between TNF-α and bone resorption. Indeed, Bertolini noted that the relative roles of interleukin-1 and the TNFs as osteoclast activating factors may depend on conditions such as duration of the leukocyte culture, antigen or mitogen used as stimulant and types of leukocytes present in the culture. (page 518, paragraph

spanning columns 1-2). Bertolini did not teach or suggest any treatment modality, including local or combinatorial administration of a TNF-α inhibitor.

Brandt

Brandt reports on the efficacy of systemic transfusions of the REMICADE® infliximab in the treatment of active ankylosing spondylitis (AS) in a small pilot study (*see* Abstract).

The Combined Teachings of Radomsky, Allali, Bertolini, and Brandt Do Not Establish A Prima Facie Case of Obviousness

(1) The Scope of the Prior Art References

To establish a *prima facie* case of obviousness, all elements of the claim must be taught by the cited references. Here, two major aspects of the claimed invention is not taught by any reference. Firstly, none of the references teach or suggest administration of an anti-resorptive agent (ARA) *into* the bone. At best, only systemic administration is suggested, and no disadvantages of systemic treatment are suggested. Second, none of the references teaches or suggests the value of the *combination* of administering a BFA and an ARA. Nor do the cited references, alone or in combination, teach or suggest any potential problem of using the BFA or the ARA alone or specific advantages of using them in combination as in the claimed invention. Therefore, the Office Action fails to show that the prior art references teach all elements of the claimed invention.

(2) The Prior Art References Teach Away From the Invention

The present invention achieves significant advantages over the teachings of the prior art because the formulations of the present invention are administered directly into an uncoupled resorbing bone (*e.g.*, a hip bone or vertebral body) and the formulations remain within the bone in an effective amount for at least one month. A person of ordinary skill in the art would not look to the teachings of the primary reference of record, Radomsky, because it teaches away from long-term administration of the formulation taught in the instant application. Radomsky

recites that "[i]f the composition persists at the site of desired bone growth for an *excessive period*, its presence at the bone site may inhibit the natural development of the bone, sometimes resulting in no bone formation at all." (Radomsky, col. 2, lines 32- 35, *emphasis added*). Radomsky merely teaches that the composition must usually persist at the site of desired bone growth for a period from about three (3) to about thirty (30) days, typically from 3 to about 14 days (Radomsky, col. 2, lines 26-31).

In contrast, the Specification of the present application teaches:

> Because the osteoporosis ("OP") involves the progressive resorption of bone in which many factors are involved, in many instances, simply providing a single dose or even a regimen over the space of a few days may not be sufficient to manage the OP...Accordingly, it is desirable for the AR and/or BF agent to remain within the bone as long as possible in a pharmaceutically effective amount (the Specification at page 39, line 26 through page 40, line 1, emphasis added).

The present invention is directed to administering the first and second formulations into the uncoupled resorbing bone, which is compatible with long-term administration. The Specification specifically states that the anti-resorptive and/or bone forming agent should preferably remain in the bone for as long as possible in a pharmaceutically effective amount (*see* the Specification at page 39, line 30 through page 40, line 1). The Specification also teaches that "continuous delivery of the AR and/or BF agent is considered to be highly advantageous." (*see* the Specification at page 40, lines 14-15). The Specification further states that "[s]ince in the case of many BF agents, it may be advantageous to provide an effective amount of the BF agent within the bone for a longer duration, there appears to be a need for a device that insures the continuous presence of the BF agent for an indefinite period", thereby reiterating the importance of long-term treatment of osteoporosis (the Specification at page 50, lines 7-14, emphasis added). Accordingly, the teachings of Radomsky that discourage one of ordinary skill in the art from implementing a long-term treatment effectively teach away from the present invention. Moreover, the teachings of Radomsky regarding short-term treatment are largely incompatible with treatment of osteoporosis where the long-term instraosseous administration of the BFA and ARA into the uncoupled resorbing osteopenic or osteoporotic bone is desired.

Furthermore, because long-term administration is particularly desired in the treatment of osteoporosis, intraosseous administration involving direct provision of the formulation into the affected bone is of particularly advantage. As the specification indicates:

> [S]ince the cortical shell of the bone comprises a relatively dense structure, this outer component of the bone may prevent the out-diffusion of the drug and so may provide a suitable depot for the osteotherapeutic drug, thereby increasing its half-life in the target bone. (the Specification at page 7, lines 8-17).

Therefore, treating an uncoupled resorbing bone by administering the formulations directly into the bone solves a previously unrecognized problem.

> (3) At the time of the invention, there was no motivation to combine the teachings of cited references to arrive at the present invention

The invention claimed in Claims 1 and 89 is directed to a therapy using a BFA and an ARA. The Federal Circuit expressly stated that: "Even where a general method that could have been applied to make the claimed product was known and within the level of skill of the ordinary artisan, the claim may nevertheless be nonobvious if the problem which had suggested use of the method had been previously unknown." *In re Omeprazole*, 536 F.3d 1361 (Fed. Cir. 2008). With respect to the holding in *In re Omeprazole*, the PTO *Examination Guidelines* state that:

> The *Omeprazole* case can also be analyzed in view of the discovery of a previously unknown problem by the patentee. If the adverse interaction between active agent and coating had been known, it might well have been obvious to use a subcoating. However, since the problem had not been previously known, there would have been no reason to incur additional time and expense to add another layer, even though the addition would have been technologically possible. This is true because the prior art of record failed to mention any stability problem, despite the acknowledgment during testimony at trial that there was a known theoretical reason that omeprazole might be subject to degradation in the presence of the known coating material. (Federal Registar, Vol. 75, No. 169, 53646 (2010): the Examination Guideline

Update: Developments in the Obviousness Inquiry after *KSR v. Teleflex*)

At the time of the invention, the specific combination of a BFA and an ARA was not known or suggested by the prior art. Nor was the problem associated with a treatment with the single agent was not known or recognized. Applicants identified this problem, as articulated in the Specification as follows:

> As shown in the Figure, the bone growth agent effectively causes bone growth to occur for a certain period of weeks. Without wishing to be tied to a theory, it is believed that administration of the BF agent causes increased bone growth, thereby offsetting the increased bone resorption caused by estrogen withdrawal, resulting in net bone gain. After this short period of weeks, however, the gradual depletion of the BF agent from the tissue (either through consumption or vascular elimination) returns the bone remodeling process to its essentially normal balanced state. After still more time, the continued depletion of the BF agent returns the bone remodeling process to a resorbing one resulting in continued bone loss. Simply, locally providing a bone growth agent to an osteoporotic bone may result in only a temporary bone gain.

Radomsky teaches a therapy using a combination of HA and a growth factor, but does not recognize the need to supplement the treatment with an ARA because Radomsky does not recognize the importance of long-term treatment and the problem of BFA depletion in the treatment of osteoporosis. In fact, Radomsky teaches away from long-term treatment of a bone fracture as discussed above. Moreover, the combined teachings of Allali, Bertolini and Brandt also fail to suggest the importance of long-term intraosseous administration in the treatment of osteoporosis or the particular advantages achieved in the claimed combinatorial therapy. Absent specific knowledge of an existing problem or recognized advantage, one of ordinary skill in the art would not have been motivated to combine the teachings of the prior art. *See In re Omeprazole*, 536 F.3d 1361 (4) (Fed. Cir. 2008).

> (4) None of the references alone or in combination teach clinical treatment of osteoporosis.

Moreover, one of ordinary skill in the art would not have been motivated to implement the teachings of Radomsky with the teachings of Allali, Bertolini and Brandt to arrive at the invention described in Claim 21 because the common knowledge in the art at the time of the invention was such that ankylosing spondylitis (AS) was a separate indication from osteoporosis. Although Allali teaches that osteoporosis is commonly associated with SpA, the authors also acknowledge that the cause of AS associated osteoporosis remains controversial (*see* Allali at page 348, right col., fourth paragraph). Among possible mechanisms suggested by the authors are an inflammatory mediator released during the course of AS, and decrease mobility of patients. The authors noted that "immobility is a well known risk factor for bone loss." *See* Allali at page 348, right col. fourth paragraph. At most, one of ordinary skill in the art would have understood that AS could be a confounding cause that might lead to osteoporosis, possibly due to, for example, lack of mobility or chronic spinal inflammation that contributes to the pathology of both AS and osteoporosis.

AS is quite different from osteoporosis in a number of ways. Unlike osteoporosis, AS is a form of inflammatory arthritis that affects the joints of the spine of both male and female patients, resulting in loss of spinal motion and fusion of the spine (*see* Brandt at page 1346, right col., first paragraph and RESULTS at pages 1348-1350; and Allali at page 347 "Patients and Method"). Further, the median age of the patients participating in Allali's AS study was thirty-five (*see* Allali at page 347, right col., "Patients and Methods") and the mean age of the patients participated in Brandt's study was thirty-six (*see* Brandt at page 1348, left col., first paragraph under RESULTS). In contrast, osteoporosis largely affects perimenopausal or postmenopausal female patients. Moreover, according to Brandt, the well-known AS-related diseases are uveitis, rheumatoid arthritis and inflammatory bowel syndrome (*see* Brandt, bridging paragraph between 1346 and 1347 and RESULTS). Unlike AS, osteoporosis was not taught to be associated with the inflammatory diseases listed above. Therefore, the teachings related to AS were far too attenuated to motivate one of ordinary skill in the art at the time of the invention to combine the teachings of Radomsky, directed to promoting bone growth, with the teachings of the references directed to treating AS, in order to arrive at the present invention. Therefore, this is a further reason why Claim 21 and its pending dependent claims were not obvious to one of skill in the art at the time of the invention.

For at least foregoing reasons, a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89 and 91-92 Under 35 U.S.C. §103(a)

Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89 and 91-92 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radomsky in view of Allali, Kitazawa *et al.* (*J. of Clin. Invest.* 94: 2397-2406 (1994); hereinafter, "Kitazawa") and Brandt.

The deficiencies of Radomsky, Allali, and Brandt with regard to combinatorial therapy and ARA administration into the bone are discussed above.

Kitazawa teaches that interleukin-1 (IL-1) receptor antagonist and tumor necrosis factor binding protein (TNFbp) administered subcutaneously decreased osteoclast formation and bone resorption in ovariectomized mice. Kitazawa teaches that TNFbp is a divalent inhibitor of TNF that binds with equal affinity to both TNF-α and TNF-β (*see* Kitazawa at page 2401, right col., final paragraph).

The teachings Kitazawa do not compensate for the deficiencies in Radomsky, Allali, and Brandt. For example, Kitazawa does not teach administration of an ARA into the bone, and Kitazawa does not suggest the problems associated with BFA or ARA diffusion/depletion, which are particularly important in treatment of osteoporosis. Further, Kitazawa does not recognize the importance of long-term treatment *via* the administration into the uncoupled resorbing bone using the BFA and ARA in combination. As noted above, the Federal Circuit stated that the invention is nonobvious if the problem which had suggested the use of the method had been previously unknown. *In re Omeprazole*, 536 F.3d 1361 (Fed. Cir. 2008). The importance of combinatorial therapy using BFA and ARA together with the direct administration into the uncoupled resorbing bone is not recognized by Kitazawa. Thus, absent specific knowledge of an existing problem or recognized advantage, one of ordinary skill in the art would not have been motivated to combine the teachings of the cited references to arrive at the claimed invention.

Further, the TNFbp employed by Kitazawa binds with equal affinity to both TNF-α and TNF-β. Based on the teachings of Kitazawa, it is largely unclear whether the positive effects observed by Kitazawa on bone resorption in ovariectomized mice was due to TNF-α or TNF-β

inhibition. Accordingly, one of ordinary skill in the art would not have been motivated to modify the teachings of Kitazawa to arrive at the claimed invention.

Therefore, the teachings of Kitazawa do not compensate for the deficiencies in Radomsky, Allali, Kitazawa and Brandt and a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 4 and 24 Under 35 U.S.C. §103(a)

Claims 4 and 24 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radomsky in view of Allali, Bertolini, Brandt and Boyle *et al.* (US 2003/0207827).

Claims 4 and 24 are directed to the method of treating post-menopausal patients and are dependent from independent Claims 1 and 21, as amended.

Boyle teaches that osteoprotegerin can be used to treat bone diseases including osteoporosis. Boyle tested administration of osteoprotegerin to inhibit the effects of IL-1 α and IL-β. Boyle teaches treatment of osteoporosis in postmenopausal women.

The deficiencies of Radomsky, Allali, Bertolini, and Brandt are discussed above. The teachings of Boyle do not compensate for these deficiencies because Boyle does not teach or suggest the problem associated with BFA or ARA early diffusion. Nor does Boyle does teach or suggest direct administration of a BFA or a monoclonal antibody that inhibits TNF-α into the uncoupled resorbing bone. Therefore, for the reasons discussed above, the combination of references does not teach or suggest the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 60 Under 35 U.S.C. §103(a)

Claim 60 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radomsky in view of Allali, Bertolini, Brandt and Trieu *et al.* (US 2002/0026244; hereinafter, "Trieu").

The Office Action states that: "It would have been obvious to the one of ordinary skill in the art at the time the invention was made to incorporate highly specific cytokine antagonist such as remicade to the teachings of Trieu since the reference teaches advantage of the same in treating osteoporosis with bone morphogenetic protein etc. One skilled in the art would have

been motivated to administer into the bone the formulation comprising the bone forming agent and remicade because Trieu et al. successfully teach local administration of implants/drug in between bones in order to treat osteoporosis" (Office Action at page 11).

Applicants respectfully disagree. Instant Claim 60 is directed to administering an effective amount of a bone forming agent and an anti-resorptive agent into the vertebral body. The vertebral body is the spinal bone itself ("vertebra"). However, Trieu's teachings are directed to placing an implant in the spinal disc by: (1) removing the natural nucleus pulposus of the intervertebral disc; and (2) placing an implants in the space created by the removal of the nucleus pulposus, as the title of the Trieu reference indicates (*i.e.*, "*Intervertebral disc nucleus implants and methods*"). Thus, Trieu's teachings are directed to placing an implant in the intervertebral disc, not *into the vertebral bone*. In contrast, the claimed invention is directed to inserting a device into the spinal bone(s) ("vertebral body"). Administration by releasing a formulation from an implant placed in between two bones (*i.e.*, two vertebrae) is not equivalent to, nor does it suggest, administration which involves delivering the formulation into the bone as in present Claim 60 due to the difference in mechanical and physiological responses. Moreover, Trieu is focused on a condition other than osteoporosis. Unlike the statement in the Office Action, Trieu does not teach or motivate one of the ordinary skill in the art to administer a therapeutic agent into the vertebral body as in Claim 60.

The combined teachings of the references do not provide any inference regarding the administration of a monoclonal antibody against TNF-α into the disc for treating an osteoporotic patient. Simply, the teachings of Trieu do not compensate for the deficiencies in the Radomsky, Allali and Bertolini references, particularly in view of their deficiencies regarding the administration of a monoclonal antibody against TNF-α into an uncoupled resorbing bone. Thus, these references would not have motivated one of ordinary skill in the art at the time of the invention to administer a monoclonal antibody against TNF-α into an uncoupled resorbing bone as elaborated above.

Finally, Applicants note that, in the Amendment filed before the Office on October 20, 2009, Claim 60 was amended to delete the elements directed to: (1) removal of a portion of the disc; and (2) insertion of a spinal implant into the disc space. As amended, Claim 60 no longer recites the elements relating to the teachings of Trieu. Thus, this amendment to Claim 60 should

have rendered the rejection moot and placed Claim 60 in condition for reconsideration. However, the comparison to Trieu in the rejection has been repeated almost verbatim in the previous Office Action and again in this present Office Action with no reference to the claim amendment and related discussion of that amendment. Applicants respectfully reiterate their request that Claim 60 be properly reconsidered in light of the amendment made on October 20, 2009.

In sum, the teachings of Trieu do not compensate for the deficiencies in the combined teachings of Radomsky, Allali and Bertolini, and one would not have been motivated to modify the teachings of Trieu to treat an osteoporotic patient by inserting an implant containing this ARA *into* the vertebral body without recognizing the specific problems and advantages identified by Applicants as discussed in the Specification as well as above. Therefore, a *prima facie* case of obviousness has not been established and the combined teachings of Radomsky, Allali, Bertolini and Trieu do not render the claimed invention obvious.

Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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